Final report to

"Development and application of modern amination methodologies in the field of oxygenheterocycles" (K75806)

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Introduction

During the last decades several new methodologies have been developed to create C-N bonds. One of these techniques is the transition metal-catalyzed coupling reaction between (hetero)aromatic halides and various nitrogen compounds such as amines, amides or nitrogen heterocycles. The most outstanding procedure is the palladium-catalyzed coupling known as Buchwald-Hartwig reaction.

Usually, aminochromones and -flavones have been synthesized by using classical methods which are often laborious and the syntheses suffer from low efficiency and synthetic limits. To our best knowledge only very few studies have been performed on the application of the Buchwald-Hartwig reaction in the field of chromones, flavones or coumarins. Only the synthesis of some flavones with amino group in their ring A4 and hexylamino unit in their ring A, B or C5 was reported. 3-Bromocoumarins were transformed into their 3-amino derivatives with primary amines, amides and sulfonamides.

Results

1. Buchwald-Hartwig and Ullmann reactions for the synthesis of substituted chromonoids, flavonoids and coumarins

One of the main directions of the research plan was the Buchwald-Hartwig and Ullmann reactions for the synthesis of substituted chromonoids,flavonoids and coumarins. In this project we successfully investigated the suitability of the palladium- and copper-catalyzed amination for producing various oxygen heterocycles with primary, secondary, tertiary amino

and N-hetaryl groups. Reaction conditions were optimized and applied for chromone, flavone and coumarin skeletons carrying other substituents in wide variety. Since such types of compounds have not been synthesized so far, the biological screen of the prepared small- and medium-size libraries allowed identifying promising potential drugs and hits. Our results was published in the European Journal of Organic Chemistry in 2015 (Kónya, K., Pajtás, D., Kiss-Szikszai, A., Patonay T. Buchwald-Hartwig reactions of monohaloflavones. *European Journal of Organic Chemistry*, **2015**, *4*, 828–839 DOI: 10.1002/ejoc.201403108). The article describes the amination of different monobromo or monochloroflavones with primary and secondary alkylamines and aniline derivatives by Buchwald–Hartwig reaction. The influence of the used phosphine ligands was described. The use of amino acid derivatives as a nitrogen source is also demonstrated. This latter reaction allows the synthesis of unique flavone–amino-acid conjugates. In summary, we have demonstrated that the Buchwald–Hartwig amination of bromoflavones with halo substituents on their aromatic rings is a useful tool for the synthesis of amine derivatives that are hardly available by previously reported methods. We have pointed out that the previously published structures of some derivatives obtained from 3-halo- or sulfonyloxyflavones with primary amines were erroneously assigned, and that in fact, ring-contracted products were formed. Palladium-catalyzed C–N bond formation also proved to be an efficient tool in the synthesis of flavone–amino-acid hybrids, although the coupling takes place accompanied by significant racemisation of the stereogenic centre.

Therefore, we decided the development of Buchwald-Hartwig amination of different bromoflavones with amino acid and peptide derivatives as nitrogen source giving unique structures. We have demonstrated the Buchwald-Hartwig amination of bromoflavones using amino acid esters as nitrogen source affording unique flavone-amino acid hybrid molecules. Although, at the beginning of the study the coupling took place with racemisation of the stereogenic center but after an extensive screening of the reaction parameters we found the way to preserve the configuration. Under these new conditions various amino acids was successfully coupled providing our hybrid derivatives in higher yields and considerable enantiomeric excesses. Furthermore, the C-N bond formation was also extended to different peptide esters giving flavone-peptide hybrid molecules. Synthesis of these unique derivatives was also demonstrated by the deprotection of flavone-amino acid hybrids followed by classical peptide synthesis. The previously observed racemisation occurring during the reaction of flavone-amino acid hybrids was successfully prevented in most cases. The biological assays of these novel structures showed cytotoxic effects on different cancer cell

lines. Our results were collected in an article, Dávid Pajtás, Krisztina Kónya, Attila Kiss-Szikszai, Petr Džubák, Zoltán Pethő, Zoltán Varga, György Panyi, Tamás Patonay: Optimization of the synthesis of flavone-amino acid and flavone-dipeptide hybrids' in Buchwald-Hartwig reaction, which was submitted in *European Journal of Organic Chemistry* in 2016.

As a continuation of our published results of the amination of 6- and 7-bromoflavone with different types of primary, secondary amines, and aniline derivatives we were interested in to use 8-bromoflavone as a substrate. However, to the best of our knowledge the synthesis of the 8-bromoflavone substrate was not published previously in a detailed way. There is some paper in which 3′-bromo-2′-hydroxyacetophenone was used as a starting material, although the preparation of this acetophenone was not solved. Therefore, we decided to investigate these problems. Our results were published in the journal Synthesis in 2016 (Pajtás, Dávid; Patonay, Tamás; Kónya, Krisztina. "Synthesis of 8-Bromoflavone and Its Buchwald–Hartwig Reaction with Amines" *Synthesis* **2016**; *48(01)*: 97-102. DOI: 10.1055/s-0035-1560325). In this paper, we have demonstrated the synthesis of 8-bromoflavone from the commercially available 2-bromophenol through 3′-bromo-2′-hydroxyacetophenone as a starting precursor. Its synthesis was optimized and the further transformation to 8-bromoflavone requires simple and convenient reaction conditions. Because the starting materials are easily accessible and the reactions give good yields, this new approach has potential applications in the synthesis of various functionalized flavones, which are of considerable interest as potential biologically active compounds or pharmaceuticals. The Buchwald–Hartwig amination of the prepared 8-bromoflavone was studied with different primary and secondary amines.

During our research work mainly two differently substituted bromocoumarins (3-bromocoumarin, 4-bromocoumarin) were studied. The syntheses of these bromocoumarins were based upon the previous experiences of our group. Several experiments were carried out between bromocoumarins and different alkyl-, arylamines without the presence of a catalyst, and their palladium catalyzed reactions were also studied.

3-Bromocoumarin was reacted with some aliphatic primary amines, and the products were isolated in medium yields. Different aromatic amines were reacted with 3-bromocoumarin without the presence of any palladium catalyst, however no transformation was detected. This unfavorable experience can be explained by the insufficient nucleophilic properties of aniline derivatives. Surprisingly, in the case of linear aliphatic secondary amines, there were no

reactions. However, the desired product can be prepared in good yields in the case of cyclic amines.

These experiments were extended to 4-bromocoumarin also, by using the previously optimized conditions. During these studies in case of primary aromatic amines revealed, there is no transformation without catalyst, whereas in the presence of a palladium catalyst the corresponding products were isolated in good yields. By applying other primary aliphatic amines, in all case the 3-aminocoumarin derivatives were isolated instead of 4-aminocoumarin one. It is also revealed that secondary aromatic amines e. g. 4-dibutylaminocoumarin can be obtained without any catalyst, but in the presence of a palladium source the yield was not increased. The reaction of the cyclic secondary amines proceeds itself in good yield, which yield can be increased with palladium catalyst.

Similar side reactions were not detected in case of Ullmann conditions. In this research field numerous of new compounds substituted with amino group were prepared. However, the workup of the Ullmann reaction of 3-bromocoumarin and aniline resulted in unexpected products (3-amino and 3-hydroxy coumarins). In general, the yields of the Buchwald-Hartwig reactions of the halocoumarins were increased compared to the yields of Ullmann reactions.

2. Electrophilic aziridination of chromenes, enol derivatives of chromanones, chalcones and coumarins

We have previously demonstrated that base-induced reactions between α-azido ketones and simple aldehydes or more complex carbonyl compounds, such as α-oxo aldehydes or α-oxo esters, provide an efficient method for the preparation of valuable tri- and tetrafunctionalized synthons. The reaction of α-azido ketones with aldehydes has been used successfully by Padwa and co-workers. A similar coupling with *in situ* generated imines using organocatalysts has also been reported. Surprisingly, little is known about the reactions of α-azido ketones, acting as carbon nucleophiles, with Michael acceptors. Phenacyl azides have been treated with strongly activated acceptors having two electron-withdrawing groups to give the expected adducts, which, in turn, are capable of eliminating nitrogen under basic conditions and cyclize to pyrroles. Therefore we planed the investigation of the Michael addition of 2-azido-(4-substituted phenyl)ethanones under basic conditions. Our results were published in Synlett in 2014 (Éva Juhász-Tóth, Gianfranco Favi, Orazio A. Attanasi, Attila C. Bényei, Tamás Patonay: α-Azido Ketones, Part 8: Base-Induced Coupling of α-Azido Ketones with a1,2-Diaza-1,3-diene as a Michael Acceptor. *SYNLETT* **2014**, *25*, 2001–2004. DOI: 10.1055/s-0033-1338655).

We studied the Michael addition of 2-azido-(4-substituted phenyl)ethanones , (adamantan-1-yl)-2-azidoethanone, 2-azido-1,2-diphenylethanone, 3-azido(thio)- chromanones, 2-azidobenzosuberone to ethyl 3-[(carbamoylimino)amino]but-2-enoate under basic conditions. When we treated 2-azido-(4-substituted phenyl)ethanones with 2.0 equivalents of diazadiene 6 in the presence of a catalytic amount (10%) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dry tetrahydrofuran at room temperature, we obtained ethyl 2-[1-[(carbamoylamino)imino]ethyl]-4-oxo-4-arylbut-2-enoates in good to excellent yields. Two of the four possible diastereomers were detected and isolated in each case.

To sum up, the reactivity of α-azido ketones under basic conditions with a diazadiene as a Michael acceptor has been demonstrated. The successful coupling provides additional examples of the usefulness of α-azido ketones as nucleophilic partners in C–C bond-forming reactions of diazadienes as Michael acceptors. Unfortunately, the adducts of acyclic α-azido ketones showed limited stability and easily lost hydrazoic acid to give the corresponding 2-{1-[(carbamoylamino)imino]ethyl}-4-oxo-4-phenylbut-2-enoates.

In the frame of this research our goal was to attain the aminohalogenation of chalcones containing protected hydroxyl group in position 2'. In the beginning, 4'-methylchalcone and 4'-chlorochalcone were employed as model compounds, and the corresponding aminochlorinated and aminobrominated product was successfully isolated with chloramine-T or bromamine-T in the presence of PIDA. The addition of NaOH in a one-pot reaction provided the appropriate aziridine derivatives in medium yields.

The aminochlorination was successfully accomplished with 2'-acetoxychalcone producing the corresponding compound in low yields. Several methods were tested to increase the yield - such as using anhydrous solvent, rising the temperature, using various catalysts - but none of these changes increased the former yield.

In case of aminochlorination of 2'-benzyloxychalcone, having this protecting group higher stability and activating effect, the product was isolated in medium yield. Furthermore, a scale-up step was successfully worked out by starting in ten times more amount. During these reactions, the formation of two diastereomers was detected by ^{1}H and ^{13}C NMR spectroscopy; unfortunately one of them was isolable as a clean product.

Finally, we made attempts to prepare flavanones by basic hydrolysis of these aminohalogenated α,β-unsaturated ketones. However, a benzofuranone derivative was produced in good yield which is in accordance with the former results of our team. As a conclusion of these results, the aminohalogenation of C=C bond of chalcones by using mild conditions can be a key step for the preparation of benzofuranone derivatives.

Summary

In the frame of this research project, we studied the palladium and copper catalyzed amination of different O-heterocycles with various primary, secondary amines. The optimization of the Buchwald-Hartwig and Ullmann reactions resulted in differently substituted chromone, flavone and coumarin derivatives. Since the synthesis of such type compounds was not solved earlier, the biological test of the prepared small and medium sized compound libraries can open the way to the identification of potent hit compounds. Since amino acids can be applied as nitrogen donor, we studied the preparation of the flavone-amino acid hybrids. These experiments were successful, too. Different haloamination and amination methods were tested with unsubstituted and 2-substitutedchalcones. These latter compounds can be used as

precursors for the preparation of the chromanones and flavanones; however our results showed benzofuranone derivatives can be produced in good yield.

Publications and conferences

In the frame of this project our results were summarized already in four articles. We showed the outcome of these experiments at national and international conferences as posters or lectures fifteen times (please see the list below).

Publications:

1. Kónya, K., Pajtás, D., Kiss-Szikszai, A., Patonay T. Buchwald-Hartwig reactions of monohaloflavones. *European Journal of Organic Chemistry*, **2015**, *4*, 828–839. DOI: 10.1002/ejoc.201403108

2. Pajtás, Dávid; Patonay, Tamás; Kónya, Krisztina. "Synthesis of 8-Bromoflavone and Its Buchwald–Hartwig Reaction with Amines" *Synthesis* **2016**; *48(01)*: 97-102. DOI: 10.1055/s-0035-1560325

3. Dávid Pajtás, Krisztina Kónya, Attila Kiss-Szikszai, Petr Džubák, Zoltán Pethő, Zoltán Varga, György Panyi, Tamás Patonay: Optimization of the synthesis of flavone-amino acid and flavone-dipeptide hybrids' in Buchwald-Hartwig reaction. **2016**, submitted in *European Journal of Organic Chemistry.*

4. Éva Juhász-Tóth, Gianfranco Favi, Orazio A. Attanasi, Attila C. Bényei, Tamás Patonay. α-Azido Ketones, Part 8: Base-Induced Coupling of α-Azido Ketones with a1,2-Diaza-1,3-diene as a Michael Acceptor. *SYNLETT* **2014**, *25*, 2001–2004 DOI: 10.1055/s-0033-1338655

National and International Conferences:

1. Juhász-Tóth, É.; Patonay, T.; Favi, G.; Attanasi, O.A.: α-Azido-ketonok bázis-indukált reakciója 1,2-diaza-1,3-butadiénekkel. (lecture), MTA Flavonoidkémiai Munkabizottság, 2009. 12. 07, Budapest

2. Juhász-Tóth, É.; Szalóki, D.; Patonay, T.: Szubsztituált bróm-kumarinok előállítása és Buchwald-Hartwig kapcsolási reakcióik tanulmányozása. (poster) MKE Vegyészkonferencia és 53. Magyar Spektrokémiai Vándorgyűlés, 2010. 06. 30. – 07. 02., Hajdúszoboszló

3. Juhász-Tóth, É.; Dihen, K.; Sipos, Z.; Patonay, T.; Favi, G.; Attanasi, O.A.: α-Azido-ketonok bázis indukált Michael addíciós reakciói. (poster), MKE 1. Nemzeti Konferencia, 2011. 05. 22-25, Sopron

4. Lukács, N.; Szalóki, D.; Juhász-Tóth, É.; Patonay, T.: Különböző helyzetben brómozott kumarinok Buchwald-Hartwig aminálása. (lecture), MTA Heterociklusos Kémiai Munkabizottság, 2011. 09. 26-28, Balatonszemes

5. Szalóki, D.; Pócsi, Zs.; Juhász-Tóth, É.; Patonay, T.: Szubsztituált aminokumarinok szintézise Buchwald-Hartwig- és Ullmann-reakciókkal. (lecture), MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság, 2012. 06. 06-08, Balatonszemes

6. Patonay, T.; Kónya, K.; Juhász-Tóth, É.; Vasas, A.; Ábrahám, A.; Nagy, G.Z.; Pajtás, D.; Kondor, Z.: Palládium- és réz-katalizált keresztkapcsolási reakciók oxigéntartalmú heterociklusok körében. (plenary lecture), MKE Vegyészkonferencia, 2013. 06. 26-28, Hajdúszoboszló

7. Juhász-Tóth, É.; Patonay, T.; Favi, G.; Attanasi, O.A.: Base-induced Reaction of α-Azido Ketones with 1,2-Diaza-1,3-butadienes. (poster) 16th European Symposium on Organic Chemistry, 12-16 July, 2009, Prague, Czech Republic

8. Kónya, K.; Pajtás, D.; Fekete, Sz.; Patonay, T.: Syntheses of Synstituted N-alkyl/ arylflavones by Palladium-catalyzed Buchwald-Hartwig Amination and by Classic Alkylation Methods. (poster) 16th European Symposium on Organic Chemistry, 12-16 July, 2009, Prague, Czech Republic

9. Kónya, K.; Pajtás, D.; Patonay, T.: C-N Bond Formation: a New Route to Flavones of Potential Pharmacological Activity. (poster) International Conference: Natural and Artificial Ecosystems in the Somes-Cris-Mures-Tisa River Basin, 7-8 May, 2010, Arad, Romania

10. Pajtás, D.; Kónya, K.; Kiss-Szikszai, A.; Patonay, T.: The Formation of Flavone-amino acid hybrids by Buchwald-Hartwig Reaction. (poster) 4th German-Hungarian Workshop "Synthesis, Isolation and Biological Activity of Natural Products and Related Systems", June 14-16, 2011, Debrecen, Hungary

11. Juhász-Tóth, É.; Dihen, K.; Sipos, Z.; Patonay, T.; Favi, G.; Attanasi, O.A.: Base-induced Michael Addition Reactions of α-Azido Ketones. (poster) 4th German-Hungarian Workshop "Synthesis, Isolation and Biological Activity of Natural Products and Related Systems", June 14-16, 2011, Debrecen, Hungary

12. Kónya, K.; Balogh, F.; Patonay, T.: Unexpected Regio- and Chemoselective Products of Reductive Amination of 3-Formylchromones. (poster) 4th German-Hungarian Workshop "Synthesis, Isolation and Biological Activity of Natural Products and Related Systems", June 14-16, 2011, Debrecen, Hungary

13. Kónya, K.; Balogh, F.; Patonay, T.: Unexpected Regio- and Chemoselective Products of Reductive Amination of 3-Formylchromones. (poster), 17th European Symposium on Organic Chemistry, July 10-15, 2011, Crete, Greece

14. Patonay, T.; Juhász-Tóth, É.; Kónya, K.: A Novel Approach to Amino-substituted Oxygen Heterocycles. (poster), 23rd International Congress of Heterocyclic Chemistry, July 31-August 4, 2011, Glasgow, UK

15. Patonay, T.; Kónya, K.; Pajtás, D.; Lukács, N.; Pócsi, Zs.; Szalóki, D.: Buchwald-Hartwig- and Ullmann-amination of Oxygen Heterocycles. (poster) BOSS 2012 International Conference on Organic Synthesis, July 1-4, 2012, Tallinn, Estonia